Deliverable 7.5

Project ID	654241
Project Title	A comprehensive and standardised e-infrastructure for analysing medical metabolic phenotype data.
Project Acronym	PhenoMeNal
Start Date of the Project	1st September 2015
Duration of the Project	36 Months
Work Package Number	7
Work Package Title	Privacy and Ethics
Deliverable Title	D7.5 Report to the EC/REA with ethical approvals, informed consent forms and patient information material of datasets to be used within PhenoMeNal e-infrastructure development
Delivery Date	M8
Work Package leader	ICL
Contributing Partners	ICL, EMBL-EBI

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1. Executive Summary

The PhenoMeNal project does not generate Metabolomics data. In order to create the projected data processing pipeline and for testing our ethical, legal and social implications (ELSI) goals, however, we need to use data sets that closely mimic the types of data which will be analysed by our future users. These test data sets (and data used by future beneficiaries of PhenoMeNal) should therefore satisfy ELSI requirements. Before using any already existing datasets, we have evaluated the associated documentation for each dataset. In particular, where data is not open and freely available, we have obtained ethical approval documentation, patient information and patient permission forms and these documents are collated in the Appendix. This information provides a firm basis on how to decide on the use cases for each of the datasets available. For example, based on the available ELSI information, some data will only be used at the host institution, where ethical approval for use at that institution is present. Open data (such as MetaboLights data, http://www.ebi.ac.uk/metabolights/) can be freely used within the terms of use of the EMBL-EBI within the consortium. The datasets described here are also reported in D9.1 (Report on existing software tools, workflows and analytical pipelines initially supported in the PhenoMeNal grid, submitted M6).

2. Project Objectives

No.	Objective	Yes	No
1	Develop appropriate policies, procedures and management accountability and structures to provide a robust governance framework for information management.	x	
2	Raise awareness of information governance within the consortium and assure on going compliance.	x	
3	Ensure that ethical standards and guidelines of Horizon2020 will be rigorously applied, regardless of the country in which the research is carried out.	x	

3. Detailed report on the deliverable

3.1. Background

PhenoMeNal will create a software environment that can process diverse ‘omics data sets with a focus specifically on human metabolomics data. The PhenoMeNal project does not generate Metabolomics data, but in order to properly develop the

software environment, a number of standard datasets will be required to test the formats, data processing pipelines, user interaction and the stability of the software and to make sure that our procedures are in line with generally accepted ELSI guidelines. For this reason, we have selected a number of use cases that typically reflect the type of data that will be used in PhenoMeNal.

To begin testing software in Phenomenal, we will initially use publically available anonymised data as this will enable timely testing of the software without the much higher level security constraints required for confidential patient data, which will nevertheless be dealt with later in the project. In D7.3, Evaluation report for the introduction of a data provider form, we have outlined our approach to data exchange in PhenoMenal, and how a data provider form will be used to allow movement of data between groups with approval within ELSI constraints. The use of this approach will be evaluated for the use of any datasets that are not open. It should be stressed that data will only be used with permission of the data provider, and we are relying on the provider to give guidance that they have obtained informed patient permission for use in Phenomenal.

It is to be noted that even the use of such publically available data is associated with ethical and legal guidelines. These datasets are listed below along with their ELSI status. For each dataset we have listed the ethical permissions, patient information forms and patient permission forms. For publically available data from the EBI MetaboLights database, we refer the reader to the EBI terms of use (http://www.ebi.ac.uk/about/terms-of-use).

This deliverable refers to Task 7.7: Identify human clinical datasets to test drive development and ensure that the ethical approvals cover use within the PhenoMeNal project, including the non-EC partner Swiss Institute of Bioinformatics (SIB). Provide EC/REA with copies of ethical approvals and related informed consent forms and information materials for patients.

3.2. Current PhenoMeNal data sets

Here we describe the current status of ethical permissions and documentation for the five use case data sets already presented in D9.1. The studies chosen, availability of suitable data and the available ELSI information on these studies is as varied as the status (open or restricted data) and the trans-national sources of the data. As PhenoMeNal matures, datasets will be added or removed depending on their suitability for testing the platform as well as the ELSI information available for the data.

Use Case 1: Analysis of the MESA research study on subclinical cardiovascular diseases.

The Multi-Ethnic Study of Atherosclerosis (MESA, http://www.mesa-nhlbi.org/) is a medical research study involving more than 6,000 men and women in the United States. The study focuses on the characteristics of subclinical cardiovascular diseases. As part of the COMBI-BIO project (Development of combinational biomarkers for subclinical atherosclerosis, http://www.combi-bio.eu/), metabolomics data was produced in two phases for 4,000 MESA participants from serum samples using NMR and LC-MS platforms. The data in this cohort:

a) Will be publically available once deposited in dbGAP (database of genotypes and phenotypes, http://www.ncbi.nlm.nih.gov/gap, expected by July 2016).
b) We currently have permission to distribute and use the data. An email from the Governance committee is attached.

Open-access data can be browsed online or downloaded from dbGaP without prior permission or authorization. For more sensitive data sets involving personal health information the download of data is allowed after registration with the site. Since the data used in PhenoMeNal will be publically available from dbGap, we will follow the Open Access protocols at:

a) http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/about.html

The study is described at:

b) https://www.mesa-nhlbi.org/aboutMESAOverviewProtocol.aspx#protocol

For use of the MESA data, we specifically requested a response from the access committee and this is attached in the Annex 6.1 (email from the coordinating committee giving permission for use for MESA data in PhenoMeNal).

The initial use of MESA data will be as an example data set to test the tools that are currently being developed. We are using a subset, the COMBI-BIO MESA data as this use-case. This data follows quite closely the workflow now being used in the National Phenome Centre and we know the data well. The purpose would be for development and testing of software/computational tools: no biological analysis will be done or published.

Use Case 2: **Analysis of the CoLaus population-based study on cardiovascular diseases and risk factors**

The main goals of this study are to obtain information on the epidemiology and genetic determinants of cardiovascular risk factors and diseases as well as mental health in the adult population of Lausanne. This data will be solely for use within PhenoMeNal as this is not a public (open) data. We are in communication with the study PI and have received ethical documentation from them. The use of the data will be behind secure firewalls and used for testing purposes of the software

processing and analysis. We do not expect to publish any biological findings. Ethical approval and patient information and consent forms are attached in Appendix 6.2.

Use Case 3: Data processing for the Uppsala Fibromyalgia study
The patient samples were collected in Norway. The original ethical approval is included in the appendix. The controls have been donated from patients in Rumania. Their consent form information in Rumanian is attached in Annex 6.3. This data will be solely for use within Phenomenal as this is not public (open) data. We are in communication with the study PI and have received ethical documentation from them. The use of the data will be behind secure firewalls and used for testing purposes of the software processing and analysis. We do not expect to publish any biological findings.

Use Case 4: Data processing, statistical analysis, and annotation of the "Physiological Variations of the Urine Metabolome"
This study is already publically available in the MetaboLights repository at the EBI with accession number MTBLS20 (http://www.ebi.ac.uk/metabolights/MTBLS20). The complete statistical processing workflow is available in Workflow4Metabolomics (http://workflow4metabolomics.org) under reference W4M00001 (http://workflow4metabolomics.org/dataset_sacurine). Since this is an open data publicly available, de-anonymised and filtered, this data does not include consent forms, ethical approval or patient information at this source. The terms of use can be visited at: http://www.ebi.ac.uk/about/terms-of-use

Use Case 5: Data processing for fluxomic analyses.
This study is deposited in the MetaboLights repository at the EBI and will become publically available during the PhenoMeNal project (data may be deposited with a future release data to allow first publication of results etc. by the depositors). Since this will be open data, publicly available de-anonymised and filtered open access data does not include consent forms, ethical approval or patient information at this source. The terms of use are at this web address: http://www.ebi.ac.uk/about/terms-of-use.

4. Delivery and Schedule

The deliverable is delayed: No

5. Background information

Patient and research subject data is very sensitive, and it is paramount to establish a robust governance framework for overall information management including sensitive data. The PhenoMeNal e-infrastructure will be able to cope with data generated from comprehensive clinical, genotypic, 'omics and analytic sources including medical records, electronic health records, clinical measurements, genotypic data, phenotypic data from tissue and biofluid analysis, image and pathology data. Primarily, all data collected and held within the project will comply with all local laws, regulations and ethics. All personal information will be processed in accordance with accepted Data
Protection Principles outlined above. Responsibility for data will be with the host Institution/data provider.

The use of patient research data in Phenomenal as a test bed for the implementation of software and algorithms was determined by the availability of the data, its usefulness in representing probable data sets and also any restrictions on use within an ELSI environment. Some of the data is open, and can be freely downloaded and used while other data has restrictions applied to it (such as only being permissible to use the data within the Phenomenal project at a particular site). We have obtained ethical approval documents, patient information data and patient permission forms and discussed with the data providers (PI's) how we will use the data and obtained permission. This approach allows us to decide whether we are using the data in a way that conforms to the ELSI of the study.

This deliverable refers to Task 7.7: Identify human clinical datasets to test drive development and ensure that the ethical approvals cover use within the PhenoMeNal project, including the non-EC partner Swiss Institute of Bioinformatics (SIB). Provide EC/REA with copies of ethical approvals and related informed consent forms and information materials for patients.

Person Month per Participant	ICL	EMBL-EBI	IPB	UB	UL	UOXF	SIB	UU
	1.5		0.2			0.4		

6. Annexes

6.1 MESA study – ethical information, patient information and forms

a) Email confirming PhenoMeNal use of MESA data.

From: Craig Johnson [mailto:wcraigj@u.washington.edu]
Sent: Monday, February 29, 2016 10:03 PM

To: David Herrington; 'David Vu'; 'Philip Greenland'; 'Ebbels, Timothy M D'
Cc: 'Kayleen Williams'; 'Glen, Robert C'; 'Pearce, Jake T M'; Gregory L. Burke; 'Russell P Tracy'; 'Jerome I. Rotter'
Subject: RE: MESA use case for PhenoMeNal?

Hi David,

MESA Steering Committee has considered and approved this use. The MESA DMDA already executed with Imperial College is still considered binding and will suffice for this additional use as well.

When Steering Committee discussed, it was noted that the version of the data available at Coordinating Center (with MESA IDs as was used for COMBI-Bio) could also be used if more convenient. David Vu made progress in applying corrections to IDs in the metabolomic data files today and expects to make additional progress with the conversion to SHARe ID in the next day or two, so we can provide access to either version of the data files.

Thank you,

Craig

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b) **Mesa Ethical Approval:** Approval of Continuing Review

NORTHWESTERN
UNIVERSITY

APPROVAL OF CONTINUING REVIEW

June 16, 2015

Kiang Liu

312-908-8307
kiangliu@northwestern.edu

Dear Dr. Kiang Liu,

On June 16, 2015, the IRB reviewed the following submission:

Determination Date:	6/16/2015
Type of Submission:	Continuing Review
Review Level:	Expedited
Expedited Category (if applicable):	- (8)(a) Long-term follow-up
Title of Study:	Multi-Ethnic Study of Atherosclerosis (MESA)
Principal Investigator:	Kiang Liu
IRB ID:	STU00021057-CR0001
Funding Source:	National Heart, Lung, and Blood Institute, Funding Source ID: R01 HL077612 National Institutes of Health, Funding Source ID: R01 HL093081 Environmental Protection Agency, Funding Source ID: RD 83169701 National Heart, Lung, and Blood Institute, Funding Source ID: N01-HC-95164
Grant ID:	R01 HL077612; R01 HL093081; RD 83169701; N01-HC-95164
IND, IDE, or HDE:	None
Documents Reviewed:	• 0324-003_EyePhotographyProtocol.pdf, Category: Protocol; • 0324-003_Protocol.pdf, Category: Protocol; • MESA E5 protocol_Includes Home Visit_clean copy, Category: Protocol;

The IRB has approved the study to continue, with an approval period of: 6/16/2015 to 6/15/2016 inclusive. Thirty days before expiration, you are to submit a continuing review for this study. You will be sent reminder notifications as your last date of approval approaches; however, you are responsible for being aware of when your approval period expires.

If continuing review approval is not granted by the end of the day on 6/15/2016, approval of this study expires.

In conducting this study, you are required to follow the requirements listed in the Northwestern University (NU) Investigator Manual (HRP-103), which can be found by navigating to the IRB Library within the eIRB+ system.

NU IRB approval does not constitute nor guarantee institutional approval and/or support. Investigators and study team members must comply with all applicable federal, state, and local laws, as well as NU Policies and Procedures, which may include obtaining approval for your research activities from other individuals or entities.

For IRB-related questions, please consult the NU IRB website at http://irb.northwestern.edu. For general research questions, please consult the NU Office for Research website at http://www.research.northwestern.edu.

Sincerely,

Heather Gipson
IRB Director

c) MESA Informed Consent description

Appendix B

MESA Exam 5
Informed Consent Template

Study Description

You are invited to participate in the fifth examination of the Multi-Ethnic Study of Atherosclerosis (MESA), a research study sponsored by the National Heart, Lung, and Blood Institute and conducted by *[PI name]* from *[Department and Institution]*. The National Eye Institute and the US Environmental Protection Agency are also supporting certain study components.

MESA is an ongoing study that includes over 6,800 participants from six centers across the country. You enrolled in MESA during July 2000 – August 2002, along with [*number*] other residents of [*location*].

Your participation in this study is entirely voluntary. You should read the information below and ask questions about anything you do not understand before deciding whether or not to participate.

Purpose of the Study

The main purpose of MESA is to study heart disease and diseases of the blood vessels beginning in the early stages. People who may have early heart disease, known as "sub-clinical" heart disease, may not know it because they feel well. MESA is studying why some people develop clinical conditions such as heart attack, heart failure, and stroke. In order to learn this information, the people in the study are being followed for many years. Over time, MESA has studied other conditions, such as lung disease and rheumatoid arthritis, and will likely include other conditions in the future.

Procedures

If you decide to participate you will be asked to undergo an examination that will require 4-9 hours of your time and which may be split into two visits. The examination will include the following procedures, most or all of which you have done before:

1. Physical Examination: You will undergo a limited physical exam in which your blood pressure, height, weight, and body size will be measured. A probe will be placed on your finger to measure the amount of oxygen in your blood (off oxygen, if you use it).
2. Health Interviews: You will be asked questions concerning previous illnesses, hospitalizations, diet, physical activity, social issues, and use of tobacco, alcohol, and medications.
3. Ankle-Arm Blood Pressure: This test involves measuring blood pressure in both arms and legs.
4. Fasting blood samples will be collected to measure blood sugar, blood fats (including cholesterol) and other substances related to the risk of disease. Up to 7 tablespoons of blood will be drawn for these tests. Samples will also be frozen and stored indefinitely for future analysis.

5. Urine will be collected for analysis. Approximately one cup will be collected, and will be frozen and stored for future analyses.
6. Electrocardiogram (ECG or EKG): This is a recording of the electrical activity of your heart. Electrodes will be placed on the skin of your chest, arms, and legs for this test.
7. Eye Exam: The purpose of this test is to find out how well you see at a distance and to take photographs of the back of your eyes to look at the blood vessels. We will ask you some questions about how well you see. We will then measure your vision. If you use glasses, we will ask you to take them off for the test and the prescription of your glasses will be measured. If you wear contact lenses, we will not ask you to take them out. We will then darken the room and place a special camera close to your eyes to photograph the back (retina) of both of your eyes. No eye drops will be used and the camera will not touch your eyes. There will be a flash of light when the pictures are taken.

In addition, you are asked to undergo the procedures next to the checked boxes:

☐ Magnetic Resonance Imaging (MRI): All participants who had this test during the first MESA exam will be asked to repeat the MRI during the present exam. The MRI exam will evaluate the size and function of your heart and nearby blood vessels. For this exam, you will need to lie still on a table and will be moved into a large device that takes pictures of your heart using magnetic fields. The exam takes 45-60 minutes. If you are a woman of childbearing age, you will have a pregnancy test to make sure that you are not pregnant before having the MRI.

All participants who have the MRI exam and who have good kidney function will be asked to receive gadolinium as part of the test. Gadolinium is an FDA approved contrast agent that allows us to see the heart and blood vessels better. It is given via a regular intravenous (IV) line, which will be placed in your arm before the test. If you agree to receive gadolinium, we will test your kidney function before the MRI to check that it is safe for you.

☐ Computed Tomography (CT) of the Arteries of the Heart: Approximately half of MESA participants will have this test. The CT scan is a special type of x-ray examination that is done to measure the amount of calcium in the arteries of your heart. You will be asked to lie on a table with just the upper part of your body inside the CT scanner. You will need to remain still and hold your breath for about 10-20 seconds during the test. If you are a woman of childbearing age, you will have a pregnancy test to make sure that you are not pregnant before having the CT scan.

☐ Carotid Ultrasound: Approximately one half of MESA participants will have this test. Ultrasound will be used to measure the size and function of the carotid arteries, which are the large arteries in the neck. You will be asked to lie on a table for this test. Gel will be applied to the skin on your neck and a small hand-held probe will be used to examine the carotid arteries on both sides of the neck.

☐ Spirometry: Participants who previously participated in the MESA Lung Study will be selected to participate in spirometry testing. Spirometry measures your lung function. It involves breathing into and out of a tube as hard and as fast as you can, three or more times. A new, clean mouthpiece is used for each participant. About one in five participants will be selected on the basis of the spirometry results for an inhaled bronchodilator (albuterol), which opens up the air passages, and repeated spirometry

testing. You will be asked some questions to assure your safety for spirometry and albuterol. Spirometry takes approximately 20 minutes.

☐ Computed Tomography (CT) of the Lungs: Participants who previously participated in the MESA Lung Study will have this test, many of whom will also get the CT of the heart. The CT scan is a special type of x-ray examination that is done to measure the amount of emphysema in your lungs. You will be asked to lie on a table with just the upper part of your body inside the CT scanner. You will need to remain still and hold your breath for about 10-20 seconds during the test. If you are a woman of childbearing age, you will have a pregnancy test to make sure that you are not pregnant before having the CT scan.

If you have one of the imaging tests listed above, you will receive a report listing the main finding (for example, amount of calcium in the arteries of the heart). The scan will be reviewed in case there are other findings that may have a major and significant impact on your health. In the unusual case of such a finding being present, it will be reported to you and, if you wish, your physician.

Follow-up Information

We will continue to contact you by phone every 6-9 months and ask you about your health since the last contact. If you are unable to answer questions yourself, we may contact a person you have named who could answer questions for you. If you are hospitalized or admitted to a convalescent or nursing home, we will ask that institution for your records. We will review the records to determine the reason for your admission and your diagnosis. We may request records from your doctor for certain office or clinic visits to determine if you have been diagnosed with one of the diseases that MESA is studying. We may also request Medicare records.

DNA Testing

Genetics, or the study of genes and gene products, has progressed rapidly since MESA began. If you gave your permission at an earlier exam, MESA collected DNA, the material that contains the genes, from your blood samples and stored it at that time. Your DNA is used to try to learn who is at increased (or decreased) risk of heart disease, stroke, or other diseases. MESA is looking at specific genes and also at a wide sampling of participants' DNA. MESA is also looking at a substance called RNA, which is closely related to DNA and may help to understand how genes work.

Researchers will read your genetic code looking for genes for heart disease and related conditions. They may also occasionally read genes that have variations known to cause other rare but serious diseases. Most people have versions of these genes that are safe and cause no disease; however, a small number of people may have a version that suggests a greater risk for these other diseases. If you were to have such a DNA finding, there would be a chance that your family members would have the same DNA finding.

Some people do not want to be told if they have such a rare but important DNA finding, especially if there is little that can be done to prevent the related disease from occurring. Other people do want this information. We will ask you your preference now in case we examine for and find such a DNA finding in the future. MESA will consult with experts to make decisions on

what DNA findings to report and how this should be done. People who do want this genetic (DNA) information will need to be tested in a second laboratory to make sure the first test was correct. They may also be advised to talk with a trained professional (a genetic counselor) about their own and their family members' risks of disease. This counseling could be important because the genetic information may be complicated and its impact on individual and family member risk can be difficult to interpret. The genetic counselor can explain the results and answer questions. MESA will provide the additional genetic testing and counseling if we examine for and find such a DNA finding.

Sharing of Data and Samples

Use of data and samples:

- Portions of samples of your blood, urine and DNA, in addition to study information and genetic data, will be stored for use by researchers indefinitely.
- The National Institutes of Health will allow researchers who qualify to analyze your data and samples. Researchers can qualify by proposing a research study approved by National Institutes of Health and by agreeing to protect your identity.
- Samples and data sent to other laboratories will be labeled only with a code number. No standard information that identifies you, such as your name, date of birth, address, etc., will be available to other researchers.

Commercial use of data and samples:

- Researchers from private companies that develop diagnostic lab tests or treatments for diseases may request access to your study information or samples. However, these researchers will not have access to personal information that identifies you, such as your name, date of birth, address, etc.
- Your samples will not be sold to any person, institution, or company and will not be used for cloning (creating body organs or tissues or fluids from your genetic material).
- Neither you nor your family would benefit financially from discoveries made using the information and/or specimens that you provide.

Genetic research:

- Very detailed information about your DNA will be stored centrally at the National Institutes of Health, where it will be shared with other investigators for research. This information and all of your other data will be used by researchers to look for genes that affect the risk of developing diseases and may lead to better methods for prevention and treatment. The stored information is de-identified, which means that identifying information such as your name, date of birth, address, etc., is removed. Access to this stored information will be controlled by the National Institutes of Health. The National Institutes of Health is committed to protecting the confidentiality of all the information it receives, but will also comply with relevant laws which might include Freedom of Information Act (FOIA) requests for de-identified information.

Confidentiality

- Any information we obtain will only be used for statistical, scientific purposes. In any report we publish or present, we will not include any information that will make it possible to identify you. Information may be released to other researchers for scientific purposes, but only after removing your name and all other personal identifiers. Research records with personal identifiers will be kept in locked file cabinets.

- To further help us protect your privacy, we have obtained a Certificate of Confidentiality from the federal government. This certificate means the researchers cannot be forced to tell people who are not connected with the study, including the courts, about your participation, without your written consent. Unless you give permission, MESA can only disclose information about you in very special cases (if you or someone else is in serious danger of harm).

Potential Risks and Discomforts

- Clinic Exam: The procedures used in this study are considered to be safe. The risks associated with the clinic exam are minimal.

- Blood Draw: Risks of drawing of a blood sample are discomfort at the site of needle insertion, bruising (black and blue discoloration) or inflammation at the site, and rarely, faintness. The bruise is usually painless and disappears within a few days.

- EKG: Minor skin irritation may occur where the EKG leads are placed on the skin.

- Eye Exam: There are no known risks associated with taking a photograph of the eye. People who are light sensitive may experience some minor discomfort from the camera flash. After the pictures are taken, you may see a blue or red spot which will disappear within 5 to 7 minutes and which causes no damage to the eye.

- DNA information: Receiving DNA information may cause anxiety. Also, some people have been worried that genetic information could be used to discriminate against them. A law was passed in 2008 by the Federal Government ("GINA" or Genetic Information Nondiscrimination Act) that prevents many forms of discrimination based on genetic information.

- Data Sharing: MESA takes extensive efforts to protect your identity and privacy. Yet, because of the large amount of information collected about you, we cannot absolutely guarantee that information about you or your blood relatives will never become known. This is partly because of the possibility of matching your DNA sample with other DNA collections (such as those kept by law enforcement agencies). **However, researchers are strictly prohibited from attempting to identify you.**

  - ☐ MRI: The MRI machine does not use ionizing radiation (like x-rays). Instead, it uses a strong magnet and radio waves to generate pictures of the body. The procedure is associated with minimal risk. You will need to wear earplugs or earphones since the machine can produce high noise levels, which may be

uncomfortable. With earplugs, the risk to hearing is insignificant. Some people may experience psychological discomfort in the scanner if they are uncomfortable in tight places (known as claustrophobia). You will be able to speak directly to the MRI technologist at all times, and the examination will be stopped at any time upon your request.

The gadolinium contrast agent is generally safe. There is a small risk of allergic reaction after the gadolinium injection, with less than a one in 300,000 chance that this will be severe. There is also a smaller risk of nephrogenic systemic fibrosis, a potentially serious and rare skin condition that can occur in patients with kidney problems. We will guard against this risk by checking your kidney function prior to the MRI and will not give gadolinium if you have low kidney function. Metallic taste in the mouth, tingling in the arm, nausea, or headache occurs in less than 1% (less than 1 in 100) people. Insertion of the needle may also cause minor pain, bruising and/or infection at the injection site.

☐ Computed Tomography of the heart: The CT scan uses x-rays to make pictures. The amount of radiation you will be exposed to during the CT scanning is less than 3 mSev, which is 6% of the yearly on-the-job exposure allowed radiation workers. Another way of understanding this is to compare the exposure from the CT to the radiation exposure you receive on average from natural sources. The radiation exposure from the CT scanning is approximately the amount of natural background radiation that the average person in the United States receives each year. The radiation in this study is not expected to measurably increase your risk of cancer. The potential lifetime cancer risk associated with the above estimated radiation is less than 3 per 10,000.

☐ Computed Tomography of the lung: The CT scan uses x-rays to make pictures. The amount of radiation you will be exposed to during the CT scanning is less than 6.5 mSev, which is 12% of the yearly on-the-job exposure allowed radiation workers. Another way of understanding this is to compare the exposure from the CT to the radiation exposure you receive on average from natural sources. The radiation exposure from the CT scanning is approximately the amount of natural background radiation that the average person in the United States receives in two years. The radiation in this study is not expected to measurably increase your risk of cancer. The potential lifetime cancer risk associated with the above estimated radiation is less than 6 per 10,000.

☐ Spirometry. Minimal or no risk. Occasionally after receiving the albuterol inhaler, a temporary sensation of "heart racing" and shakiness may develop. This will resolve quickly.

All of the tests, particularly imaging studies (MRI and CT), may identify abnormalities for which you may be recommended to have additional testing. You will be referred to your own doctor for follow-up of all medical information obtained by the study and you, or your insurance company, will be responsible for those costs. MESA will not pay for these tests, except for additional genetic testing and genetic counseling if you are found to have a potentially important DNA finding and wish to be told about it.

Benefits

One benefit of participating in this study is getting results from some medical tests at no cost. (These tests, like the entire study, are paid for by the National Institutes of Health and other agencies.) Information from the tests will be given to you and your doctor, if you want. However,

please keep in mind that these tests are being performed for research purposes and not to diagnose any specific medical conditions. Also, the MESA study is not intended to provide medical care or interfere with your relationship with your own doctor. If you do not have your own doctor, you can be referred to one if you want.

The information learned from this study will increase scientific knowledge about the causes of early heart disease and diseases of the blood vessels, as well as other conditions.

Costs and Payments

There are no costs associated with participating in this study. You will not be paid for participating in this study. However, you will be reimbursed a total of $___ for time and transportation expenses for the exam.

Participants in the Lung Substudy will be reimbursed $___ for the time to complete spirometry and the CT scan of the lung.

OR

There are no costs associated with participating in this study. You will be reimbursed for out of pocket expenses incurred in connection with coming to the clinic.

Withdrawing consent

- You may withdraw your permission for anyone to use your health information (data and samples) at any time. To do this, send a written notice to the investigator in charge of the study at the following address:

  _____

  _____

- If you decide to leave the study, you may request that your records, test results, blood samples, and DNA be removed from the study to the extent possible.

Statement of Exam 5 Consent:

I agree to participate in this examination and to allow researchers to store and analyze my data and blood and urine samples, in a way that will not identify me, for the research described above. I understand that these responses will replace those on my previous informed consent if answered differently. I will receive a copy of this consent form.

Furthermore, I agree to the following:

Consent for Sharing of Information with Health Care Provider:

I agree that MESA may share findings important to my health from MESA Exam 5 tests and examinations with my doctor.

- ☐ Yes, share my results
- ☐ No, do not share my results

Consent to Obtain DNA for Research

I agree to allow MESA to obtain additional DNA at this exam for research purposes. This will allow researchers to read my genetic code in detail and to see if my genetic code is related to diseases I now have or may develop in the future.

- ☐ Yes, obtain my DNA for research purposes
- ☐ No, do not obtain my DNA

Request to be Notified, or Not, of Possible Important Genetic Findings

I wish to be notified if results indicate I may have a genetic finding that is known to greatly increase risk of an important disease (CHECK ONE). Please note that very few MESA participants will be checked for these rare genetic findings at present; however a larger number of MESA participants may be checked in the future.

- ☐ Yes, but only if a treatment to prevent or lessen the disease is known
- ☐ Yes, even if no treatment or prevention is known
- ☐ No, do not notify me

Consent for Use of Gadolinium for the MRI of the Heart

I agree to have the gadolinium injection as part of the MRI scan of my heart

- ☐ Yes, I consent to the gadolinium injection
- ☐ No, I do not wish to have the gadolinium injection

Consent for Lung Substudy

I agree to participate in the Lung Substudy to study lung structure and function and their impact on the heart. I understand that the results of spirometry and the CT scan of the lung will be sent to me and, if I so indicated above, to my physician. I also understand that information and samples that I have provided or may in the future provide to MESA (for example, responses to questionnaires, data from CT scans, and genetic materials) may be analyzed for studies of lung disease in MESA.

- ☐ Yes, I consent to participant in the Lung Substudy
- ☐ No, I do not wish to participant in the Lung Substudy

With my signature I also am giving permission for my hospital and/or health clinic to release any of my health records that MESA needs and requests. This permission has no expiration date.

Signature of Participant	Date
Signature of Person Obtaining Informed Consent	Date
Signature of Investigator	Date

Optional Consent Form Language as Required/Desired at Specific Sites

1) For sites requiring reporting of imaging study incidental findings to participants:

Incidental Finding

The CT and MRI exams you are having as part of this research study are not the same as clinical exams. They are designed to answer specific research questions. The exams will be reviewed by a qualified person and read to an appropriate standard. The research studies are not a replacement for clinical studies and often less comprehensive.

There is a possibility that while reviewing your CT and MRI we may see a finding that we did not expect to see in this study. If this finding might be significant to your immediate health we will report this to you. This is what is called an "incidental finding."

We will let you know (INSERT or your legal representative if appropriate for the study) if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, we will make every effort to contact you in a timely manner.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding.

If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance.
- The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

2) For reintroducing MESA Air to participants who did not previously join:

All participants in MESA either have been or will be asked to participate in the Air Pollution study. This study involves a questionnaire, which asks about characteristics of your place of residence, such as type of heating, and how much time you spend indoors, outdoors, or commuting. This questionnaire also asks about your work environment if you have not yet retired. The questionnaire takes about 20 minutes. We will use information based on your address and your responses to the questionnaires to estimate the air pollution levels at your home and at other places where you spend your time. This will involve assigning geographic codes (geocodes) to all the addresses that you provide to us.

Consent to Participate in the Air Pollution Study I agree to allow my data originally collected for the MESA study (including clinical information, biological specimens and

DNA) to be used in conjunction with this Air Pollution Study. I also agree to allow the use of my geocoded address and Air Questionnaire responses in the air pollution assessment.
□ Yes, I agree to participate
□ Do not agree

3) For sites that wish to adapt the main study consent template to include language for MESA participants who will be newly recruited into MESA Air (rather than to develop a separate ancillary study consent form for this):

In the first paragraph of the consent form, after "Environmental Protection Agency" add "(MESA-Air)." MESA-Air could also be mentioned in its own sentence. In the second paragraph, insert "or" plus the dates of MESA Air recruitment after "2002".

Remember to include a checkbox indicating consent to participate in MESA Air.

4) For sites whose IRBs require consent for commercial use of data and samples:

Consent to permit data and samples to be used for commercial purposes
□ Yes, I agree that my data and samples may be used for commercial purposes
□ Do not agree

5) For sites that are participating in MESA COPD (Columbia, JHU, NWU, UCLA):

The following paragraphs will replace the corresponding paragraphs in the consent template:

Under "Procedures":

☐ Spirometry: Participants who previously participated in the MESA Lung Study or who have lung disease will be selected to participate in spirometry testing. Spirometry measures your lung function. It involves breathing into and out of a tube as hard and as fast as you can, three or more times. A new, clean mouthpiece is used for each participant. About one in five participants will be selected on the basis of the spirometry results for an inhaled bronchodilator (albuterol), which opens up the air passages. You will be asked some questions to assure your safety for spirometry and albuterol. Spirometry takes approximately 20 minutes.

☐ Computed Tomography (CT) of the Lungs: Participants who previously participated in the MESA Lung Study or who have lung disease will have this test, many of whom will also get the CT of the heart. The CT scan is a special type of x-ray examination that is done to measure the amount of emphysema in your lungs. You will be asked to lie on a table with just the upper part of your body inside the CT scanner. You will need to remain still and hold your breath for about 10-20 seconds during the test. If you are a woman of childbearing age,

you will have a pregnancy test to make sure that you are not pregnant before having the CT scan.

The following paragraph should be added to the "Procedures" section:

☐ Six minute walk: Two hundred participants in the MESA Lung Study or who have lung disease will be asked to perform this test. You will be asked to walk for 6 minutes on a level surface to see how far you can go. If you use oxygen when you walk, you will use it for this test.

The Following paragraph should be added to the "Possible Risks and Discomforts" section:

☐ Six Minute Walk Test. Risks of this test include shortness of breath and chest tightness, and rarely, faintness or heart problems. We will guard against these by asking you questions before the test.

6) For sites that that wish to include a paragraph about total radiation:

The following paragraph may be added after the two Computed Tomography paragraphs under Potential Risks and Discomforts:

☐ Computed Tomography of both the heart and lung: If you have both of these scans, the amount of radiation you will be exposed to during the CT scanning is less than 9.5 mSev, which is 18% of the yearly on-the-job exposure allowed radiation workers. The potential lifetime cancer risk associated with the above estimated radiation is less than 9 per 10,000.

Only one of the three paragraphs should be checked.

6.2 CoLaus study - ethical permission, patient information and forms

a) **Ethical Approval**

English summary for ethical approval

CoLaus-2: Ref-Nr: 33/09, approval date: 06.03.2009

UNIVERSITY OF LAUSANNE

FACULTE DE MEDECINE
COMMISSION D'ETHIQUE
DE LA RECHERCHE CLINIQUE
RUE DU BUGNON 21-CH-1005 LAUSANNE

Faculty of Medicine
Ethics Committee for Clinical Research
RUE DU BUGNON 21-CH-1005 LAUSANNE

Lausanne, le 6 mars 2009
Lausanne, 6. March 2009

Avis de la Commission d'Ethique de la recherche clinique
Protocole 33/09 :
CoLaus 2 (=follow-up de l'Etude CoLaus)
Extension du protocole 16/03

Opinion of the Ethics Committee for Clinical Research
Protocole 33/09
CoLaus 2 (=follow-up of CoLaus study)
Extension of protocole 16/03

Investigateur:
Dr P. Vollenweider, PD & MER
Investigator:
Dr P. Vollenweider, PD & MER

La Commission d'Ethique arrête l'avis suivant :
A - Avis positif

The Ethics Committee agrees on the following advice :
A - Positive Decision

UNIL | Université de Lausanne
Décanat de la Faculté de biologie et de médecine
Rue du Bugnon 21
CH-1011 Lausanne

COMMISSION D'ETHIQUE
DE LA RECHERCHE CLINIQUE
RUE DU BUGNON 21-CH-1011 LAUSANNE

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PRESIDENT

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PRESIDENT PROF. F. STIEFEL
TEL. : +41 21 314 02 34

Prof. Peter Vollenweider
Médecin Chef
Service de médecine
CHUV
1011 Lausanne

Lausanne, le 6 mars 2009
MB/fch

Avis de la Commission d'Ethique de la recherche clinique

Monsieur et cher Collègue,

Lors de sa séance du **23 février 2009**, la Commission d'Ethique de la recherche clinique, Sous-Commission I (composition détaillée en page 4) a procédé à une évaluation approfondie du projet de recherche désigné ci-après :

Protocole 33/09 : Cardiovascular diseases and Psychiatric disorders in the general population : a prospective follow-up study
CoLaus 2 (=follow-up de l'Etude CoLaus)
Extension du protocole 16/03

Investigateur :

Prof. Peter Vollenweider
Médecin Chef
Service de médecine
CHUV
1011 Lausanne

English summary for ethical approval

CoLaus-3: Ref-Nr: CER 26/14 approval date: 11.04.2014

CANTON DE VAUD

Commission Cantonal d'éthique de la recherché sur l'être humain
Ave de Chailly 23
1012 Lausanne

Cantonal Ethics Committee for Research on human being
Ave de Chailly 23
1012 Lausanne

Lausanne, le 11 mars 2014
Lausanne, 11. March 2014

Avis de la Commission cantonale (VD) d'éthique de la recherche sur l'être humain
Protocole 26/14 :

Opinion of the Cantonal Ethics Committee for Research on human being
Protocole 26/14

Investigateur principal:
Dr P. Vollenweider, PD & MER

Principal Investigator:
Dr P. Vollenweider, PD & MER

La Commission d'Ethique arrête l'avis suivant :
A - Avis positif

The Ethics Committee agrees on the following advice :
A - Positive decision

Type de procédure:

☐ procédure ordinaire ☐ ré-évaluation ☐ procédure ordinaire CED

☒ procédure simplifiée ☐ Avis présidentiel ☐ Avis présidentiel CEL

La Commission arrête l'avis suivant:

☒ **positif**[1]

☐ **avis conditionnel**[2] (conditions à remplir avant approbation)

- ☐ Les documents révisés seront réévalués en procédure ordinaire (nombre de copies: 13)
- ☐ Révision des documents et information écrite à la Commission d'éthique (nombre de copies: 1)
- ☐ Entretien avec la Commission

☐ **négatif**[3] (motivé)

☐ **avis justifié de ne pas entrer en matière**[4]

.....

signifie

[1] L'étude peut être soumise aux autorités fédérales compétentes (Swissmedic / OFSP / OFEFP) pour notification. L'étude peut être entreprise (s'il s'agit d'une étude non régie par la Loi sur les produits thérapeutiques, la Loi sur la transplantation, la Loi relative à la recherche sur les cellules souches ou l'Ordonnance sur la radioprotection).

[2] Les documents concernés doivent être révisés avant soumission à la Commission d'éthique. L'étude ne peut ni débuter ni être notifiée avant d'avoir obtenu l'avis positif de la Commission d'éthique.

[3] Dans sa forme actuelle, l'étude ne peut pas être mise en route.

[4] La CE n'est légalement pas compétente pour évaluer cette étude. Soit une autre CE est habilitée à l'évaluer, soit l'étude ne nécessite pas d'approbation par une CER.

Remarques :

- La CER atteste qu'elle accomplit son travail conformément aux recommandations ICH-GCP.
- Veuillez SVP retourner à la CER le rapport final au plus tard un an après la fin de l'étude (cf page 3)
- Droit de recours dans le cadre de la Commission d'éthique.
- L'avis s'applique également aux autres investigateurs(trices) mentionné(e)s dans la demande d'évaluation qui travaillant dans des sites de recherche relevant du champ de compétence de la CER (doivent figurer sur une liste séparée).

Prof. Roger Darioli
Président de la séance

AGEK / CT CER

Arbeitsgemeinschaft der Schweizerischen Forschungs-Ethikkommissionen für klinische Versuche
Communauté de travail des Commissions d'éthique de la recherche en Suisse

canton de vaud

Commission cantonale d'éthique de la recherche sur l'être humain
Av. de Chailly 23, 1012 Lausanne

Prof. P. Francioli, Président
Prof. R. Darioli, Past-President

Secrétariat central
Tél. 021 316 18 30/31/32/33
Fax 021 316 18 37
E-mail: secretariat.cer@vd.ch

Prof. Peter Vollenweider
Médecin chef
Service de médecine interne
CHUV
Bugnon 46
1011 Lausanne

Lausanne, le 11 mars 2014
RD/ns

Avis de la Commission cantonale (VD) d'éthique de la recherche sur l'être humain

Monsieur,

Après réception des réponses à nos questions du 4 février 2014, ainsi que des documents révisés et désignés ci-après, la CE vous fait part de son avis :

Protocole 26/14 : Maladies cardiovasculaires et troubles de l'humeur dans la population lausannoise: étude de suivi/CoLaus 3

Investigateur(trice) principal:
Prof. Peter Vollenweider
Médecin chef
Service de médecine interne
CHUV
Bugnon 46
1011 Lausanne

Documents reçus le 11 mars 2014 :

15. Votre lettre du 10.03.2014
16. Réponses aux questions de la CE
17. Protocole, version du 10.03.2014 avec modifications et version finale
18. Feuille d'information, version du 10.03.2014 avec modifications et version finale
19. Formulaire de consentement, version du 10.03.2014 avec modifications et version finale.

N° de réf. de la CER-VD 26/14 – Prof. Peter Vollenweider 11.03.2014

Type de procédure:

☐ procédure ordinaire ☐ ré-évaluation ☐ procédure ordinaire CED

☒ procédure simplifiée ☐ Avis présidentiel ☐ Avis présidentiel CEL

La Commission arrête l'avis suivant:

☒ **positif**[1]

☐ **avis conditionnel**[2] (conditions à remplir avant approbation)

- ☐ Les documents révisés seront réévalués en procédure ordinaire (nombre de copies: 13)
- ☐ Révision des documents et information écrite à la Commission d'éthique (nombre de copies: 1)
- ☐ Entretien avec la Commission

☐ **négatif**[3] (motivé)

☐ **avis justifié de ne pas entrer en matière**[4]

.....

signifie

[1] L'étude peut être soumise aux autorités fédérales compétentes (Swissmedic / OFSP / OFEFP) pour notification. L'étude peut être entreprise (s'il s'agit d'une étude non régie par la Loi sur les produits thérapeutiques, la Loi sur la transplantation, la Loi relative à la recherche sur les cellules souches ou l'Ordonnance sur la radioprotection).

[2] Les documents concernés doivent être révisés avant soumission à la Commission d'éthique. L'étude ne peut ni débuter ni être notifiée avant d'avoir obtenu l'avis positif de la Commission d'éthique.

[3] Dans sa forme actuelle, l'étude ne peut pas être mise en route.

[4] La CE n'est légalement pas compétente pour évaluer cette étude. Soit une autre CE est habilitée à l'évaluer, soit l'étude ne nécessite pas d'approbation par une CER.

Remarques :

- La CER atteste qu'elle accomplit son travail conformément aux recommandations ICH-GCP.
- Veuillez SVP retourner à la CER le rapport final au plus tard un an après la fin de l'étude (cf page 3)
- Droit de recours dans le cadre de la Commission d'éthique.
- L'avis s'applique également aux autres investigateurs(trices) mentionné(e)s dans la demande d'évaluation qui travaillant dans des sites de recherche relevant du champ de compétence de la CER (doivent figurer sur une liste séparée).

Prof. Roger Darioli
Président de la séance

b) Consent Forms

Policlinique Médicale Universitaire

IUMSP
Institut Universitaire de médecine sociale et préventive

Etude CoLaus
Prof. Gérard Waeber, responsable local
Dr. Peter Vollenweider, responsable local
BH- 10. 614 - CHUV

Study ID : RES 11120
Site ID : 52523
Subject ID : _____

Formulaire de consentement

Ma signature ci-dessous indique que :

- J'ai lu le formulaire d'information et le projet de recherche m'a été expliqué.
- J'ai eu l'occasion de discuter du projet de recherche et de poser des questions.
- J'ai eu le temps de réfléchir si je désire ou non prendre part à cette étude.
- J'accepte volontairement de prendre part à cette étude.
- J'ai été informé que je suis libre de me retirer de cette étude à n'importe quel moment et que tous les échantillons sanguins seront détruits. Cela n'aura aucune conséquence sur les soins médicaux qui me seront donnés à l'avenir.
- J'accepte que les chercheurs du groupe d'étude local, de l'Université de Lausanne, des sociétés privées qui sponsorisent le projet, telles que GSK et d'autres chercheurs pourront soumettre des demandes de brevets et utiliser les brevets associés aux résultats, aux documents et aux développements issus de l'étude. J'ai été informé qu'il n'y a aucun projet de compensation financière pour les participants à cette étude.

J'accepte que mon médecin traitant soit informé des résultats de mes analyses cliniques : oui ☐ non ☐

J'accepte d'être contacté pour d'autres études à l'avenir, sous réserve d'une nouvelle autorisation de la Commission d'éthique: oui ☐ non ☐

J'aimerais être informé sur le développement de l'étude : oui ☐ non ☐

Nom du participant *: _____* (Veuillez écrire en majuscules)

Signature du participant : _____ Date :_____
(jours/mois/année)

Personne obtenant le consentement du participant :
Je confirme avoir expliqué le contenu de cette étude au participant et je confirme également qu'à ma connaissance j'ai répondu à toutes les questions posées par le participant.

Nom : _____ ***(Veuillez écrire en majuscules)***

Signature : _____Date :_____
(jours/mois/année)

Poste : _____

Document1CE_19février2003

c) Patient Information

Formulaire d'information pour les participants

1. Raisons et objectifs de l'étude

Les maladies cardiovasculaires comme l'infarctus du myocarde, les attaques cérébrales font partie des maladies les plus courantes de notre société et sont une cause important de mortalité. De nombreux facteurs peuvent augmenter le risque de développer des maladies cardiovasculaires, dont une tension artérielle élevée (l'hypertension), le tabac, le diabète, l'obésité, une histoire familiale de maladies cardiovasculaires et le manqué d'exercice. Alors que certains de ces facteurs de risque dépendent du style de vie (tabac, exercice, nutrition) d'autres ont une composante génétique importante (hypertension, diabète). Afin de mieux comprendre l'influence des facteurs de risque et de découvrir de nouveaux gènes impliqués dans les maladies cardiovasculaires, il est nécessaire d'étudier des populations de grande taille et homogènes. Les objectifs de cette étude sont :

a) De faire une enquête sur les facteurs de risque cardiovasculaires au sens large d'une
population homogène telle que Lausanne,

b) D'étudier le matériel génétique (l'ADN) et les marqueurs (protéines et lipides, comme
le cholestérol) associés aux facteurs de risque cardiovasculaires au sens large et aux
maladies associées tels que l'hypertension, le diabète, l'obésité et des troubles de l'humeur.

Nous espérons recruter 6000 participants à Lausanne.

L'étude sera menée par des chercheurs du Centre Hospitalier Universitaire Vaudois (CHUV) et de l'Université de Lausanne en association avec GlaxoSmithKline (GSK).

2. Que devrais-je faire si j'accepte de prendre part à cette étude ?

Si vous acceptez de participer à cette étude, nous vous ferons remplir un questionnaire sur vos antécédents médicaux, les antécédents médicaux de votre famille, votre état de santé actuel ainsi que vos traitements en cours et votre origine ethnique. Nous mesurerons votre poids, votre taille, et votre tension artérielle. Nous vous demanderons de donner un échantillon de 50 ml de sang à jeun, ainsi qu'un échantillon d'urine de 10 ml. Le materiel génétique (ADN) sera extrait de votre sang et les marqueurs seront mesurés dans votre sang et votre urine. Finalement, nous vous demanderons si vous acceptez que nous prenions contact avec vous à l'avenir pour répondre à certaines questions sur votre santé et votre tension artérielle.

3. Quels sont les risques?

Les risques physiques et l'inconfort associés à la prise de sang sont les mêmes que pour n'importe quel prélèvement de sang et peuvent comprendre un hématome ou une inflammation locale.

2

4. Quels sont les avantages pour moi ?

Nous mesurerons votre tension artérielle, votre taux de cholestérol, de triglycérides et de glucose (sucre) dans le sang et le médecin responsable de l'étude vous

communiquera les résultats de ces analyses. Il n'y aura aucun avantage direct immédiat pour vous si vous participez à cette étude. Toutefois, en participant à cette étude vous nous aiderez à mieux comprendre les facteurs de risque responsables de certaines maladies cardiovasculaires. Il se peut que vous aidiez également les générations à venir en faisant avancer nos connaissances sur ces maladies et le traitement de personnes atteintes de maladies cardiovasculaires et des maladies associées. Si vous êtes d'accord, nous vous informerons périodiquement du progrès des recherches qui découleront de ce projet.

5. Mes données personnelles seront-elles traitées confidentiellement?

Données personnelles : Dans cette étude tous vos renseignements personnels tels que votre nom et votre adresse seront sauvegardés séparément (c'est à dire mis sous clé dans des endroits séparés) des données médicales, des données de laboratoire et des résultats de l'analyse génétique. Ces données seront codées par un numéro et pas par votre nom. Seuls le médecin de l'étude et le personnel directement rattaché à l'étude pourront associer votre numéro de sujet à votre nom. Vos données personnelles ne seront pas divulguées aux personnes qui analysent le matériel génétique. Confidentialité : Si vous être d'accord, nous informerons votre médecin traitant de votre participation à cette étude et nous lui ferons parvenir les valeurs de votre tension artérielle et les résultats des analyses de cholestérol, de triglycérides et de glucose sanguin. Nous demanderons également à votre médecin traitant de nous fournir les résultats de votre tension artérielle avant votre participation à cette étude. Votre nom ne figurera sur aucune publication ni aucun rapport sur cette étude. En acceptant de participer à ce projet, vous autorisez des personnes accréditées de vérifier le bon déroulement de l'étude et d'examiner des données médicales ou des résultats pouvant vous concerner. Ces personnes comprennent des membres de la Commission d'Ethique locale, les autorités locales, les personnes qui collaborent avec la compagnie pharmaceutique qui sponsorise le projet ou ses partenaires. Données génétiques: Votre échantillon et vos informations médicales seront codés au moyen d'un numéro de participant et non par votre nom. Les chercheurs associés à cette étude à Lausanne, ainsi qu'à GlaxoSmithKline et ses partenaires auront accès à ce matériel et aux renseignements codés mais à aucun renseignement d'identification personnel tel que votre nom. Comme les échantillons auront été codés, il ne vous sera pas possible de connaître les résultats de l'analyse de votre ADN. Votre médecin traitant ne connaîtra pas non plus les résultats de l'analyse.

Vos données médicales et tous les résultats seront saisis dans un ordinateur et entreposés dans une base de données électronique. Vos données et vos résultats médicaux pourront être envoyés à des chercheurs travaillant pour compagnie pharmaceutique partenaire du projet. Ces données codées seront sauvegardées et traitées selon les lois en vigueur pour protéger la confidentialité des personnes participant à des projets de recherche.

3

6. Qu'adviendra-t-il des informations médicales et des échantillons que je fournis ?

En cédant aux investigateurs la possession des échantillons vous leur cédez aussi la

propriété de ces derniers. Vous conservez néanmoins le droit de déterminer le sort de ces échantillons qui ne seront pas l'objet d'autres utilisations que celles qui sont nécessaires aux fins de la présente étude. Le matériel génétique (ADN) sera prélevé des cellules contenues dans le sang que vous donnerez. Afin d'obtenir suffisamment d'ADN pour permettre une analyse complète, certaines cellules seront immortalisées, c'est à dire qu'elles seront cultivées et se multiplieront dans un laboratoire. Comme ces cellules continueront à croître, il y aura davantage de matériel génétique à étudier. De cette façon, vous n'aurez pas à retourner au site pour donner des échantillons de sang supplémentaires.
Les échantillons et les données médicales seront envoyés aux Etats Unis ou en Grande-Bretagne pour les analyses génétiques nécessaires aux fins de la présente étude. Le matériel génétique, les échantillons de sang et les lignées cellulaires seront entreposées par la société de produits pharmaceutiques qui sponsorise cette étude. Les échantillons seront conservés pour une période de 50 ans à la suite de quoi ils seront détruits.

7. Ma participation est-elle volontaire ? Que se passera-t-il si je ne veux plus participer à l'étude ?

La participation à cette étude est entièrement volontaire. Vous pouvez décider d'y participer et vous retirer de l'étude à n'importe quel moment. Si vous décidez de vous retirer de cette étude, vous n'êtes pas tenu d'en fournir les raisons et aucune de ces décisions n'influencera les soins médicaux qui vous seront donnés par la suite. Au cas où vous vous retireriez de cette étude, tous les échantillons seront détruits y compris tout le matériel génétique et les lignées cellulaires. Toutefois, les chercheurs et leurs collaborateurs conserveront toutes les données médicales récoltées jusque-là, sauf si vous vous y opposez. Le cas échéant, votre autorisation sera sollicitée à ce moment-là.

8. Puis-je être exclu(e) de cette étude ?

Vous pourrez être exclu(e) de cette étude au cas où le personnel de l'étude déciderait que vous ne remplissez pas les critères d'inclusion. Dans certains cas particuliers, vos données médicales et vos échantillons pourront ne pas être utilisés et seront détruits. Ceci pourrait se produire si il y a un nombre insuffisant de participants ou si l'étude est interrompue pour d'autres raisons.

9. Serais-je rémunéré(e) pour ma participation à cette étude ?

Non, vous ne serez par rémunéré pour votre participation à cette étude mais vos frais de déplacement - selon le tarif des transports publics - pour vous rendre au centre de recrutement ou pour vous garer près du centre de recrutement seront couverts.

4

10. Est-ce que je bénéficierai financièrement de cette étude ?

Vous ne bénéficierez pas financièrement de cette étude. En acceptant de participer à cette étude, vous donnez votre accord pour que les chercheurs rattachés à cette étude ainsi que leurs partenaires dans le secteur privé puissent utiliser les résultats et les documents de cette recherche, et tout développement ou invention issus de cette recherche à des fins commerciales et/ou de propriété intellectuelle. Il n'y a aucune intention de vous offrir, en tant que participant à la recherche, une compensation financière quelconque découlant des développements ou des

inventions issus de cette recherche. En signant ce formulaire vous acceptez que les chercheurs associés à cette étude, y compris des sociétés de produits pharmaceutiques et autres sociétés privées puissent faire des demandes de brevets sur la base des développement issus de cette recherche, étant précisé que ce ne seront pas les éléments biologiques prélevés sur vous qui seront comme tels objets de ces
brevets.

11. Quels sont les développements potentiels futurs de cette étude ?

Cette étude devrait nous permettre d'avoir une bonne estimation de la fréquence des facteurs de risque cardiovasculaires dans la population de Lausanne actuellement. Mais les conséquences à l'avenir de ces facteurs de risque sur la santé représentent aussi un point important. Nous aimerions éventuellement, dans le cadre d'une nouvelle étude, pouvoir connaître comment se développe votre état de santé au cours de ces prochaines années. Si tel devait être le cas et si vous êtes d'accord, nous prendrions alors contact avec vous par écrit. Toute sollicitation pour un nouveau projet sera faite avec l'accord de la Commission d'éthique.

Vous pouvez nous contacter si vous avez des questions sur cette étude, sur vos droits ou si vous désirez vous retirer de l'étude.

Dr. Peter Vollenweider
Département de Médecine Interne
CHUV
1001 Lausanne
Tel: 021 314 09 46

English Version (Google Translate).

1
Information Form for participants

1. Reasons and objectives of the study Cardiovascular diseases such as myocardial infarction, stroke are among the most common diseases of our society and are an important cause mortality. Many factors can increase the risk of developing cardiovascular disease, including high blood pressure (hypertension), tobacco, diabetes, obesity, family history of cardiovascular disease and lack Exercise. While some of these risk factors depend on the lifestyle (tobacco, exercise, nutrition) others have a strong genetic component (hypertension, diabetes). To better understand the influence of risk factors and to discover new genes involved in cardiovascular disease, it is necessary to study populations large and homogeneous. The objectives of this study are:

a) Undertake a survey of cardiovascular risk factors in the broad sense of homogeneous population as Lausanne,

b) To study the genetic material (DNA) and markers (proteins and fats, as cholesterol) associated with cardiovascular risk factors at large and related diseases such as hypertension, diabetes, obesity and disorders mood.

We hope to recruit 6,000 participants in Lausanne.

The study will be conducted by researchers at the Centre Hospitalier Universitaire Vaudois (CHUV) and the University of Lausanne in association with GlaxoSmithKline

(GSK).
2. What should I do if I agree to take part in this study? If you agree to participate in this study, we will complete a questionnaire about your medical history, medical history of your family, your state current health and your current treatment and your ethnicity. We will measure your weight, height, and blood pressure. We ask you to give 50 ml sample of fasting blood and a urine sample of 10 ml. Equipment genetic (DNA) will be extracted from your blood and markers will be measured in your blood and urine.
Finally, we will ask you if you agree that we contact you in the future to answer some questions about your health and tension blood.
3. What are the risks?
Physical risks and discomfort associated with the blood test are the same as for any blood sample and may include hematoma or local inflammation.
2
4. What are the advantages for me?
We will measure your blood pressure, cholesterol, and triglyceride glucose (sugar) in the blood and the doctor responsible for the study will contact you Results of these analyzes. There will be no immediate benefit to you if you participate in this study. However, in this study will help us better understand the risk factors responsible for cardiovascular diseases. You may also help future generations by advancing our knowledge about these diseases and treating people with diseases cardiovascular and related diseases.
If you agree, we will inform you periodically of the progress of research that will result from this project.
5. My personal data be treated confidentially?
Personal data: In this study all your personal information such as your name and address will be saved separately (ie locked up in separate locations) medical data, laboratory data and results genetic analysis. These data will be encoded by a number and not by name.
Only the study doctor and staff directly attached to the study can associate your subject number in your name. Your personal data will not be disclosed to those that analyze the genetic material.
Privacy: If you agree, we will inform your doctor of your Participation in this study and we will send him the values of your blood pressure and the results of analysis of cholesterol, triglycerides, blood glucose. We also ask your doctor to provide us with the results of your blood pressure before participating in this study. Your name will not appear on any publication nor any report on this study. By agreeing to participate in this project, you allow accredited persons to verify the success of the study and examine medical data or results that may concern you. These people include members of the local Ethics Committee, the authorities local, people who collaborate with the pharmaceutical company sponsoring the project or its partners.
genetic data:
Your sample and your medical information will be coded by a number of participant and not by name. The researchers involved in this study in Lausanne, as well at GlaxoSmithKline and its partners will have access to this material and information coded but no personal identification information such as your name. As samples

have been encoded, it will not be possible to know the results of analyzing your DNA. Your doctor does not know the results of analysis.
Your medical data and all results are entered into a computer and stored in an electronic database. Your data and your medical results will be sent to researchers working for pharmaceutical company partner project. These coded data will be stored and processed according to the laws in force protecting the privacy of individuals participating in research projects.
3
6. What will it medical information and samples I provided?
By yielding to the investigators possession of the samples you have transferred them also property thereof. You still retain the right to determine the fate of these Samples that will not be subject to other uses than those required for the purposes of this study. The genetic material (DNA) will be charged cells contained in the blood you give. In order to obtain sufficient DNA for enable a complete analysis, some cells will be immortalized, ie they will be grown and multiply in a laboratory. As these cells continue to grow, there will be more genetic material to study. Like this, you will not have to return to the site to give blood samples additionally.
The samples and medical data will be sent to the United States or in Great Brittain for DNA analysis necessary for this study. The genetic material, blood samples and cell lines will be stored by the pharmaceutical company sponsoring the study. The samples will be retained for a period of 50 years after which they will be destroyed.
7. My participation is voluntary it? What will happen if I do not want participate in the study? Participation in this study is entirely voluntary. You can decide to participate and withdraw from the study at any time. If you decide from this study, you are not required to provide reasons and none of these decisions influence the medical care that will be given later. In case you would withdraw you from this study, all samples will be destroyed including all genetic material and cell lines. However, researchers and
Contributors retain all medical data collected so far, unless you you oppose it. If necessary, your permission will be sought at that time.
8. Can I be excluded (e) of this study?
You can be excluded (e) of this study if the study staff decide that you do not meet the inclusion criteria. In special cases, your medical data and samples will not be used and will be destroyed. This could occur if there is an insufficient number of participants or if the study is interrupted for other reasons.
9. Will I be paid (e) for my participation in this study?
No, you will not be paid for by your participation in this study but your costs movement - depending on the price of public transport - to get to the center of recruitment or to park near the recruitment center will be covered.
4
10. Do I will receive financially from this study?
You do not financially benefit from this study. By agreeing to participate in this study, you consent to the researchers from this study and their partners in the private sector to use the results and documents This research and development or any invention resulting from this research purposes commercial and / or intellectual property. There is no intention to offer in

As a research participant, any financial compensation arising developments or inventions resulting from this research. By signing this form you agree that researchers involved in this study, including companies pharmaceuticals and other private companies can make requests patents on the basis of development from this research, given that it will not be the biological elements taken you to be such objects as these patents.
11. What are the potential future developments of this study?
This study should allow us to have a good estimate of the frequency of cardiovascular risk factors in the population of Lausanne today. But the consequences for the future of these health risk factors also represent a important point. We would possibly as part of a new study,
to know how to develop your health over the next years. If that were the case and if you agree, we would then Contact you in writing. Any request for a new project will be made with the agreement of the Ethics Commission.

You can contact us if you have questions about this study or your rights
if you wish to withdraw from the study.

Dr. Peter Vollenweider
Department of Internal Medicine
CHUV
1001 Lausanne
Tel: 021 314 September 46

6.3 Uppsala Fibromyalgia study

a) Ethical Approval for the study

REGIONAL KOMITE FOR MEDISINSK FORSKNINGSETIKK

Helseregion II

Cand.med.
Lars Tanum
Psykosomatisk avdeling
Rikshospitalet

Deres ref.: 1/10-96 **Vår ref.:** S-96192 **Dato:** 04.11.96

En dobbel blind, randomisert, placebo-kontrollert, multisenter studie for å undersøke effekten av paroxetin (Seroxat®) mot fibromyalgismerter.
Prosjektleder: Universitetsstipendiat Lars Tanum, Universitetet i Oslo og Psykosomatisk avdeling, Rikshospitalet.

Komitéen behandlet prosjektet i sitt møte torsdag 31. oktober 1996 og gjorde slikt vedtak:

"Det må opplyses i pasientinformasjonen hvorfor fenfluramintesten gjennomføres. Det bør også opplyses at en slik test kan være ubehagelig.

For øvrig har komitéen ingen innvendinger mot at prosjektet gjennomføres."

Vi ønsker lykke til med prosjektet.

Komitéen ønsker å få tilsendt revidert pasientinformasjon til orientering.

Komitéen går ut i fra at prosjektleder underretter sponsor om komitéens vedtak. Komitéen har vanligvis ikke korrespondanse med sponsor.

Med vennlig hilsen

Ola P. Hole, e.f.
avdelingsleder

Kopi: SLK

Forskningsparken, Gaustadalleen 21, 0371 Oslo, tlf 22 95 87 99, fax 22 69 84 71

Statens legemiddelkontroll
The Norwegian Medicines Control Authority

Side/antall 1/1

Avdeling/Seksjon/Saksbehandler
Medisinsk/ K. Viken

Vår dato: 26.11.96
Vår referanse: 96/02816
Deres dato: 03.10.96
Deres referanse:

Novo Nordisk Pharma AS
Postboks 24
1351 RUD

Dr. Lars Tanum
Psykosomatisk avd.
Rikshospitalet
0027 OSLO

SEROXAT - KLINISK UTPRØVING (SLKNR 96-02816)

Vi viser til Deres melding om klinisk utprøving av Seroxat ved fibromyalgi, mottatt 07.10.96.

Vi har ingenting imot at forsøket startes, men vil gjerne ha avklaring på følgende punkter:

- De statistiske beregningene er angitt å bygge på resultatene fra en pilotstudie. I protokollen refereres det også til en annen studie med større pasientpopulasjon (pkt. 3.1.5.). Er resultatene fra disse to studiene så samsvarende at det derfor kun refereres pilotstudien når tidligere resultater skal legges til grunn for beregning av pasientantall?

- I studien tillates dosetitrering opp til 80 mg Seroxat daglig. Dette er ikke i samsvar med anbefalt dosering i godkjent preparatomtale og doseringen som er benyttet i tidligere studier av Seroxat ved fibromyalgi i Norge. Vi vil be om en begrunnelse for dosevalget.

- Før studien igangsettes ved det enkelte senter må signert tilleggsskjema for senteret sendes Statens legemiddelkontroll.

Vi imøteser Deres svar.

Søknaden om godkjenningsfritak er innvilget (kopi vedlegges).

Vi beklager den lange saksbehandlingstiden, og ønsker lykke til med studien!

Med vennlig hilsen
STATENS LEGEMIDDELKONTROLL

Kjersti Viken e.f.
cand. pharm.

VEDLEGG/1

Kopi: Regional komité for medisinsk forskningsetikk, Helseregion II

9602816A.DOC

Skriv adresseres til SLK/avdeling, ikke enkeltpersoner

Adresse	Telefon	Telefax	Bankkonto	Postgiro
Sven Oftedals vei 6 N-0950 OSLO	22 89 77 00 International +47 22 89 77 00	22 89 77 99 International +47 22 89 77 99	1600 40 78997	0802 5141270

b) Informed consent form
Universitatea de Medicina si Farmacie „Iuliu Hatieganu" Cluj Napoca
Sef Lucr. Dr Constantin Bodolea

Foaie de Consimtamant Informat

Acord de donare si utilizare in scop stiintific a unei probe biologice de lichid cefalorahidian si singe.

Stimate Doamna, Stimat Domn,
Prin prezentul document informativ va solicitam acordul pentru donarea unor esantioane de lichid cefalorahidian (1-3 mL) si singe (5 mL) in scopul depistarii unor posibile complicatii postoperatorii, amelioarea tratamentului postoperator al dumneavostra si al altor pacienti.

Scopul recoltarii probelor biologice:
Scopul nostru este de a depista existenta unor compusi care circula in singe sau lichidul cefalorahidian si a caror aparitie ar putea fi corelata cu dezvoltarea unor complicatii postoperatorii. Cunoasterea acestor substante ar putea ajuta la depistarea rapida si tratamentul complicatiilor. Probele recoltate vor fi analizate in laboratoare foarte performante din Romania sau Suedia.
In cazul in care Dumneavoastra decideti participarea la acest studiu, trebuie sa stiti si sa fiti de acord cu urmatoarele:

- Se vor recolta 5 ml de singe venos prin punctia unei vene periferice.
- Odata cu punctia rahidiana ("in coloana") prin care se injecteaza anestezicul local pentru anestezia subarahnoidiana (anestezia asa zis "in coloana"), se vor recolta maxim 3 mL de lichid cefalorahidian.
- Dorim sa va asiguram ca acest volum de lichid cefalorahidian extras este foarte mic si nu exista nici un risc de complicatii prin extragerea lui.
- **Participarea la studiu NU va modifica in nici un mod tratamentul care oricum v-ar fi fost acordat (tipul de anestezie, operatie sau tratament postoperator). Refuzul de a dona aceste esantioane de lichid cefalorahidian sau singe NU va modifica in nici un fel tratamentul Dumneavoastra.**
- **De asemenea, donarea acestor probe nu este insotita de vreun beneficiu financiar.**
- Identitatea Dvs. NU va fi divulgata, probei de singe si de lichid cefalorahidian le va fi acordat un Cod de inregistrare. Singele si lichidul cefalorahidian vor fi depozitate in congelatoare speciale, insemnate cu etichete cu numar si fara datele Dvs personale (nume, adresa, etc).

Singura persoana detinatoare a datelor Dvs de identitate este Direcorul de proiect din partea Universitatii de Medicina si Farmacie Cluj-Napoca Dr. Constantin Bodolea.

- **Consimtamintul Dvs. va fi obtinut atit verbal cit si in scris prin semnatura de acord, pe acest formular de accept al donarii probelor biologice.**

Protocol de recoltare si investigatie.

I.In ziua dinaintea sau in cea a operatiei odata cu obtinerea acceptului de participare, se vor culege urmatoarele date :

1.Datele demografice: virsta, greutatea, inaltimea, sexul

2.Probele de laborator uzuale

3.Bolile asociate, terapia curenta, istoricul consumului de alcool si/sau alte droguri, fumat.(vezi Anexa I)

4.Clasa de risc anestezic ASA (American Society of Anaesthesiologists)

5.Existenta unor tipuri anume de durere acuta sau cronica

II.Preoperator se vor recolta 5 ml singe pentru examinari de laborator specifice (biomarkeri).

III.Punctia subarahnoidiana va fi realizata dupa tehnica standard. (vezi anexa II)

III. Vor fi inclusi in cercetare numai pacientii care vor fi operati in anestezie subarahnoidiana, socotita ca fiind cea mai potrivita interventiei chirurgicale propuse si care accepta donarea a 3 mL de lichid cefalorahidian.

IV. Se vor inregistra complicatiile postoperatorii si consumul de analgezice in primele 24 ore postoperator.

Va multumim.

Sunt de acord sa particip la cercetare,

Semnatura pacientului Semnatura medicului instructor

English Translation (Google Translate)

University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca
Lecturer. Dr Constantin Bodola

Informed Consent sheet

Agreement for scientific donation and use of biological samples of cerebrospinal fluid and blood.

Dear Ladies and Gentlemen,
We hereby consent to donation information we request some samples of cerebrospinal fluid (1-3 mL) and blood (5 mL) in order to detect possible postoperative complications, postoperative treatment of relief of your and other patients.

The purpose of harvesting biological samples:
Our goal is to recognize the existence of compounds that circulate in the blood or cerebrospinal fluid and whose appearance could be correlated with the development of postoperative complications. Knowledge of these substances could help early detection and treatment of complications. Samples will be analyzed in laboratories in Romania or Sweden high performance.
You decide if participating in this study, you must know and agree to the following:
- It will yield 5 ml of venous blood through a vein puncture.
- With spinal puncture ("column") which injects local anesthetic for subarachnoid anesthesia (anesthesia so-called "column"), will be collected within 3 mL cerebrospinal fluid.
- We want to assure you that this volume of cerebrospinal fluid extracted is very small and there is no risk of complications by extracting it.
- Participation in the study will not alter in any way the treatment anyway would have been granted (type of anesthesia, surgery or postoperative treatment). Refusing to donate these samples of cerebrospinal fluid or blood will not change in any way your treatment.
- The donation of these samples is not accompanied by any financial benefit.
- Your identity will not be shared, sample blood and cerebrospinal fluid will be given a registration code. Blood and spinal fluid will be stored in special freezers, marked with numbered tags without your personal data (name, address, etc). The only person holding your identity data is Direcorul project from the University of Medicine and Pharmacy Cluj-Napoca Dr. Constantin Bodola.
- Your Consent will be achieved both verbal as well as written by the signature of agreement on this form accept the donation of biological samples.

Protocol for cleaning and investigation.
I.In or the day before surgery with getting agreeing to participate, will collect the following data:
1. demographic: age, weight, height, sex

2. usual laboratory
3. associated current therapy, history of alcohol and / or other drugs, smoking. (See Annex I)
4. anesthetic risk ASA (American Society of Anaesthesiologists)
5. specific kinds of acute or chronic pain

II. Pre-operator 5 ml blood will be collected for specific laboratory exams (biomarkers).
III.Punctia subarachnoid will be conducted by standard technique. (See Annex II)
III. They will participate in research only patients who will have surgery in subarachnoid anesthesia, reckoned as the most appropriate surgery and accepting the proposed donation of 3 mL of cerebrospinal fluid.
IV. Will be recorded postoperative complications and analgesic consumption in the first 24 hours postoperatively.

Thank you.

I agree to participate in research

Signature doctor, patient, instructor